## REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1 and 3-17 will be pending in the application subsequent to entry of this Amendment. New claim 17 is added directed to preferred aspects of the disclosure, namely that ST1326 and metformin are both used in subpharmaceutical doses.

Election/Restriction/Status of the Claims

In the Official Action the examiner has shifted amended claims 3-8, formerly in Group II (as listed in the Official Action of August 9, 2007) to Group III. These claims are all directed to methods of treatment and applicants request that these claims be rejoined once the composition claims are determined to be patentable.

Response to Rejections Under 35 USC §112, Second Paragraph

In items 5-7 the examiner questions the terms "subpharmacological", "subpharmaceutical" and "pharmacological" the meanings of these terms as understood by one having ordinary skill in this art. The terms used are relative and that would be relative to the "pharmaceutical" dose versus lower amounts. The specification itself provides ample guidance to the skilled reader and the definitions of "pharmacological" and "subpharmacological" can be clearly understood by the person with ordinary skills by looking at the data shown in the Examples of this application.

In particular, at page 15 of the specification, it is indicated that the "pharmaceutical" dose for ST1326 is 100 mg/kg/day, while for metformin is 900 mg/kg/day. The comparative test of table 3 (page 18) shows that doses lower than the "pharmaceutical" doses, i.e. the "subpharmacological" doses, which correspond to 30 mg/kg for ST1326 and 200 mg/kg for metformin, have a very small effect on the reduction of blood glucose levels (mg/dl).

On the contrary, the combination of ST1326 and metformin, at "subpharmacological" doses (30 mg/kg for ST1326 and 200 mg/kg respectively), leads to a strong reduction of glucose levels.

This result demonstrates that the synergistic serum-glucose-lowering activity of ST1326 and metformin is accomplished when they are both at "subpharmacological" doses.

Therefore, it is clear from the specification what the applicant intended as the scope of the invention as stated in claims 10-13 by including the terms "pharmacological" and "subpharmacological". In view of the above, the applicant respectfully traverses this objection.

Reconsideration and withdrawal of this objection is requested.

Response to Prior Art-Based Rejection

The balance of the Official Action (items 8-11) relates to a single prior art-based rejection of alleged obviousness over one of the Giannessi references in combination with one or the other of the Giannessi references in combination with two secondary references. Specifically, the examiner argues that it is obvious to combine the teachings of WO9959957, which discloses a general formula also including ST1326 among many compounds and its hypothetical combination with other compounds, such as biguanides, together with Dagogo-Jack which discloses that metformin and many other biguanides can be used for the treatment of diabetes, to obtain the solution proposed in the present invention.

WO9959957 gives the following pharmacological data for ST1326:

- $IC_{50}$ of inhibition CPT-1 curve in rat liver mitochondria (Table 1 value 0.75 μM/l);

- 13-hydroxybutyrate and glucose serum concentration in 24 hours-starved rats, after one hour from intraperitoneal treatment, (ST1326 doses 14.5 mg/2 ml/kg)

and does not indicate ST1326 as a most preferred embodiment.

The person skilled in the art would not find any suggestion in WO9959957 to choose ST1326 from the large number of compounds of formula (I) and to specifically combine it with metformin, one of the many possible biguanides.

The data reported in the present application, showing comparative tests between the combination and the two components alone, demonstrate the synergic effect of the combination and thus establishes non-obviousness.

The synergic effect is demonstrated by the results for the combination ST1326 30 mg/kg - metformin 200 mg/kg shown in table 3, table 4, table 5 and table 6 wherein the reduction of glucose is greater than the single components alone.

In particular, table 3 shows that the combination lowers levels of blood glucose in mice in feeding conditions and 15 hours after the last treatment to 287.3 mg/dl whereas metformin alone

does not lower the blood glucose in respect to the control and metformin lowers it to 376.3 mg/dl.

Table 4 shows that the combination lowers the glucose blood levels in mice in post-absorption conditions and 8 hours after the last treatment to 362.7 mg/dl (the control is 517.7 mg/dl); on the contrary, ST1326 does not influence the levels and metformin alone lowers the blood glucose levels to 433.7

Table 5 shows the results for mice in post-absorption conditions and 6 hours after the last treatment: the control is 360.2 mg/dl, the treatment with the claimed combination lowers the blood glucose levels to 269.9 mg/dl whereas ST1326 is inactive and metformin lowers the levels to the value of 337.8.

This data are confirmed by the results shown in table 6.

In view of the above the skilled person would not be encouraged to combine ST1326 with metformin at concentrations lower than those usually employed in pharmacological treatment.

The skilled person would not be suggested to use concentrations of either drug lower than their well known published pharmaceutical doses (ST1326 = 100 mg/kg/day, metformin = 900 mg/kg/day) and to combine the two active agents since the prior art does not suggest that they could have a synergic effect when used in combination.

It is again emphasized that the skilled person to possible arrive at the claimed combination would be forced to combine and experiment with every single compound disclosed in WO9959957 with each of the biguanides known in the art, without any indication of the possible result achieved by the present invention.

Also the combination of WO9959957 and Giannessi 2003 and/or Dagogo-Jack cannot lead the skilled person to the present invention without an undue burden of experimentation. It is strongly underlined that while Dagogo-Jack gives a list of possible combinations with practical guidelines on their implementation, there no suggestion on the combination of a biguanide with a CPT-I inhibitor.

Therefore, among the many possibilities provided by the prior art, there is no teaching or suggestion of the specific combination of a single, specific biguanides, metformin, with a single specific CPT-I.

The evidence of unexpected results as shown by the data provided in the originally filed specification provide sufficient basis for demonstration of a surprising and synergistic effect provided by the combination of ST1326 and metformin – even at subpharmaceutical doses. The results presented in the original specification accompanied by the executed declaration signed by the inventors would have significant evidentiary weight, comparable to the weight given to an executed declaration. It is well established by the Federal Circuit that "the examiner must consider comparative data presented in the specification which is intended to illustrate the claimed invention in reaching a conclusion in regard to the obviousness of claims." *In re Margolis,* 785 F.2d 1029, 228 U.S.P.Q. 1123, 1129 (Fed. Cir. 1993).

For the above reasons it is respectfully submitted that claims 1 and 9-17 define inventive subject matter and that claims 3-8 should be rejoined and all pending claims allowed.

Respectfully submitted,

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